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EDITORIAL:

Vagus Nerve Stimulation for Treatment-Resistant Depression

Jerrold F. Rosenbaum and George R. Heninger

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Vagus Nerve Stimulation (VNS) for Treatment-Resistant Depressions: A Multicenter Study

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Vagus Nerve Stimulation: A New Tool for Brain Research and Therapy

Mark S. George, Harold A. Sackeim, A. John Rush, Lauren B. Marangell, Ziad Nahas, Mustafa M. Husain, Sarah H. Lisanby, Tal Burt, Juliet Goldman and James C. Ballenger

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EDITORIAL

Vagus Nerve Stimulation for Treatment-Resistant Depression

As criteria for the diagnosis of treatment-resistant depression (TRD) do vary, so do the estimated prevalence rates, but it is indisputable that patients who do not respond, poorly respond, and no longer respond to available antidepressant therapies represent a substantial minority of those with major depressive disorder (MDD). These individuals bear the burden of inescapable misery. Current therapeutic approaches include multiple sequential trials of combinations of psychotropic drugs, psychotherapies, electroconvulsive therapy, and, rarely, psychosurgery. A successful intervention in this disorder is one of the most gratifying outcomes in medicine. The possibility of a new remedy for this condition is indeed a welcome one.

In this issue Rush and colleagues present prospective but open data on the efficacy in TRD of a novel therapeutic intervention for psychiatry, vagus nerve stimulation (VNS) as delivered by the NeuroCybernetic Prosthesis (NCP) System. Approved by the FDA in 1997 for management of medically refractory partial-onset seizures, the device has also been widely available in Europe and has been used in over 6000 patients to decrease seizure frequency, often as a last alternative to surgery.

Two major drivers in psychopharmacologic development, epilepsy and serendipity, combined to play a key role in the identification of this potential antidepressant intervention. The observation of mood improvement in patients treated for seizure disorders set the stage for a treatment trial of VNS in TRD. Thus, VNS recapitulates some elements of antidepressant treatment evolution. Electroconvulsive therapy, arguably the best available intervention for TRD, resulted from observations of mood improvement after seizures in epileptics, and the most prescribed class of mood stabilizers for bipolar and related disorders is, of course, anticonvulsants. As with antidepressants themselves, which evolved from agents first developed for other conditions, the initial biological effects of VNS are evident, but the ultimate mechanism alleviating symptoms is as yet undiscovered. Once again there appears to be a latency to response, suggesting that the treatment is initiating a process of adaptation leading to eventual benefit rather than targeting the specific pathophysiology of the disorder directly. Similar also to earlier interventions, however, is the hope and possibility that study of the treatment mechanism will shed light on new places to look for the blueprint of the biology of MDD. In fact, studies of VNS in animal models of depression are being planned (J. Weiss, personal communication, December 15, 1999).

Given the excitement among clinicians, sufferers, and scientists about a potential therapeutic advance for a treatment-resistant disorder, and despite the considerable "circumstantial" evidence for efficacy, colleagues must abide for now with some circumspection until efficacy is established. It is true that many signs are positive: the unexpected mood improvement in epileptics treated with VNS (unassociated with change in seizure frequency); positron emission tomography studies revealing activation of limbic structures; neurochemical findings suggesting influences on serotonin, norepinephrine, γ-aminobutyric acid, and glutamate (our "usual suspects"); neuronal pathways that link vagal afferents eventually to the amygdala and infralimbic cortex; and evidence that locus ceruleus (LC) function is involved with VNS effects (Krahl et al 1998). The current report extends the optimism for psychotropic potential from these earlier observations by reporting improvement in 40% of a sample of 30 MDD patients with chronicity and recurrence, combined with multiple adequate treatment failures. The reason to be at least temporarily skeptical is of course the track record of many promising psychiatric treatments when matched against the daunting challenges of placebo and subject/rater blinding. The potency of a placebo that combines novelty, surgery, and electrical stimulation is likely to be quite high, but no doubt mitigated to some extent by a chronic and refractory condition. Still (and we are speaking from experience with this clinical population), placebo and blinding can be a recipe for disappointment. The good news is that a multicenter, controlled trial is planned.

The NCP System for delivering VNS (Shachter and Saper 1998) is a nifty device that has the advantage of several thousand patient years of experience. It does require surgery, a procedure similar to implanting a pacemaker in a pouch in the left chest wall and approaching the left vagus nerve in the neck, as with an endarterectomy, to attach the lead. A connection is made between device and lead by tunneling subcutaneously. Stimulus parameters can be refined and the device operated remotely. Although the intensity of stimulation determines the degree of comfort, most patients find a dose they can tolerate without having to drop out of treatment, and an external magnet allows the patient to transiently suspend the stimulus when it is uncomfortable or interferes with function. Hoarseness of voice is the most common complaint, but throat or other pain, cough, and dyspnea also can occur. Surgical complications are a risk, of course, but

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are typically transient. No dropouts due to adverse events are reported in the Rush et al (2000) trial. The long-term consequences of vagus stimulation remain to be observed, but benefits may accrue, such as the possibility of other psychotherapeutic targets, possible synergistic effects with other treatments, and evidence of improvement in word recognition memory with the treatment (Clark et al 1999).

Left vagus stimulation is thought to have minimal impact on cardiac function, less than that of right vagus stimulation, but as noted in the review by George and colleagues, transient asystoles lasting 10–20 sec have been observed during implantation. Further, since the device has been widely used in severe, treatment-refractory epilepsy, sudden deaths have occurred, but no more, and possibly less, than the number predicted as a consequence of sudden unexpected, unexplained death in epilepsy (Annegers et al 1998).

Only five of 30 subjects were considered complete responders. At a cost per device of over $9000, and when additional costs of surgery and management are considered, the price of this outcome could be estimated at between $300,000 and $600,000 to generate the five full responders. At these prices benefits surely need to be sustained, and the evidence presented suggests this to be the case for both the full and partial responders. The NCP System is generally covered by third parties for epilepsy, a hopeful predictor of coverage if the device establishes efficacy in TRD. Needless to say, predictors of response would greatly improve the cost–benefit analysis; furthermore, early identification of good candidates for VNS could avoid repeated failed trials of other interventions, leading to cost savings. On the other hand, for the patient with TRD, living the one life he or she has been issued, calculations of therapeutic possibility replace those of cost.

The important clinical findings will now stimulate research into the mechanism of the antidepressive effects of VNS. It will be important to determine which of the complex array of VNS effects are shared by the anticonvulsant and antidepressant actions. The laboratory animal models available to study anticonvulsant mechanisms have more validity and more reliable end points than animal models of depression. With these models and selective lesions in specific pathways in combination with systemic or local pharmacologic interventions, it should be possible to clarify the central anticonvulsant mechanisms involved.

The vagus nerve has a large percentage of afferent sensory fibers (over 80%) that terminate in the nucleus of the solitary tract. This in turn projects to many brain areas, including the main norepinephrine-containing nucleus, the LC, and the parabrachial nucleus, which have extensive projections to all levels of the forebrain. It is interesting that LC lesions or inactivation of the LC by lidocaine reverse the seizure-attenuating effects of VNS, suggesting that the noradrenergic system is an important part of the anticonvulsant effects (Krahl et al 1998). This is supported by the finding that VNS enhances retention of memory in humans (Clark et al 1999) and that, at least in rats, vagal efferents are not involved in the effect (Clark et al 1998). Activation of the LC via vagal mechanisms (i.e., colon distention) involves both corticotrophin-releasing factor and excitatory amino acids (Lechner et al 1997). Whether or not the LC is a major factor in the antidepressant effects will be an important discovery. It is interesting that the vagus nerve may be involved in the short-term improvement of depressed patients' moods following endotoxin administration, which increases plasma cytokines (Bauer et al 1995), since many brain responses to intravenous cytokines are dependent in part on the vagus nerve (Fleshner et al 1998).

With the use of VNS for the treatment of epilepsy, it has been possible to study VNS-induced changes in regional cerebral blood flow and a variety of neurochemical measures in cerebrospinal fluid. Some idea of the essential factors can be obtained through comparison of responders with nonresponders. A similar process can be used with VNS as a treatment for depression. It will be very interesting to observe whether or not VNS produces the same physiologic and behavioral changes in both the epileptic and depressed patients. Just as the discovery of the monoamine oxidase inhibitors led to the monamine theories of depression, the effectiveness of VNS will now stimulate progress in developing the anatomic and neurophysiologic aspects of antidepressant action.

The reports by Rush et al and George et al are received with enthusiasm for the promise they hold for psychiatry, tempered by scientific skepticism. That controlled trials and animal studies are in the offing is of considerable importance for establishing efficacy and understanding mechanism of action. For now, compassionate use in selected TRD patients—those with the greatest chronicity and severity and multiple aggressive antidepressant trial failures—appears justified.

Jerrold F. Rosenbaum

Department of Psychiatry
Massachusetts General Hospital
15 Parkman Street
WAC 812
Boston, MA 02114-3117

George Heninger

Department of Psychiatry
Yale University School of Medicine
34 Park Street
New Haven, CT 06510

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Vagus Nerve Stimulation (VNS) for Treatment-Resistant Depressions: A Multicenter Study*

A. John Rush, Mark S. George, Harold A. Sackeim, Lauren B. Marangell, Mustafa M. Husain, Cole Giller, Ziad Nahas, Stephen Haines, Richard K. Simpson, Jr., and Robert Goodman

Background: *Vagus Nerve Stimulation (VNS) delivered by the NeuroCybernetic Prosthesis (NCP) System was examined for its potential antidepressant effects.*

Methods: *Adult outpatients (n = 30) with nonpsychotic, treatment-resistant major depressive (n = 21) or bipolar I (n = 4) or II (n = 5; depressed phase) disorders who had failed at least two robust medication trials in the current major depressive episode (MDE) while on stable medication regimens completed a baseline period followed by NCP System implantation. A 2-week, single-blind recovery period (no stimulation) was followed by 10 weeks of VNS.*

Results: *In the current MDE (median length = 4.7 years), patients had not adequately responded to two (n = 9), three (n = 2), four (n = 6), or five or more (n = 13) robust antidepressant medication trials or electroconvulsive therapy (n = 17). Baseline 28-item Hamilton Depression Rating Scale ($HDRS_{28}$) scores averaged 38.0. Response rates (≥50% reduction in baseline scores) were 40% for both the $HDRS_{28}$ and the Clinical Global Impressions—Improvement index (score of 1 or 2) and 50% for the Montgomery–Åsberg Depression Rating Scale. Symptomatic responses (accompanied by substantial functional improvement) have been largely sustained during long-term follow-up to date.*

Conclusions: *These open trial results suggest that VNS has antidepressant effects in treatment-resistant depressions.* Biol Psychiatry 2000;47:276–286 *© 2000 Society of Biological Psychiatry*

Key Words: Vagus Nerve Stimulation (VNS), treatment-resistant depression, bipolar disorder, electrical stimulation

*See accompanying Editorial, in this issue.

From the Departments of Psychiatry and Neurosurgery, University of Texas Southwestern Medical Center, Dallas (AJR, MMH, CG); the Departments of Psychiatry, Radiology, and Neurosurgery, Medical University of South Carolina (MSG, ZN, SH) and Ralph H. Johnson Veterans Hospital (MSG), Charleston, South Carolina; the Departments of Psychiatry, Radiology, and Neurosurgery, Columbia College of Physicians and Surgeons, and New York State Psychiatric Institute, New York (HAS, RG); and the Departments of Psychiatry and Neurosurgery, Baylor College of Medicine, Houston, Texas (LBM, RKS).

Address reprint requests to A. John Rush, Department of Psychiatry, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75235-9086.

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Introduction

Depression is a prevalent, disabling, and often chronic or recurrent psychiatric condition costing the United States economy more than $40 billion per year, of which $12.4 billion are direct treatment costs (Greenberg et al 1993). The 6-month prevalence of depression in the general population is about 5% (Depression Guideline Panel 1993a). Three hundred forty million people worldwide, 18 million of them in the United States, suffer from depression at any one time. Further, depressive episodes usually recur over time, with the risk for further episodes proportional to the number of prior episodes. From 5% to 15% of major depressive episodes last longer than 2 years. Up to 1.5% of the general population suffer chronic or severe depressions (Depression Guideline Panel 1993a; Lopez and Murray 1998). Up to 15% of all people with severe depressions requiring hospitalization eventually commit suicide (Depression Guideline Panel 1993b; Guze and Robins 1970).

Treatment for depression aims at achieving complete symptom remission and complete restoration of day-to-day function, as well as prevention of relapses (return of current episode) and recurrences (new episodes). Numerous antidepressant medications and several forms of empirically documented, time-limited psychotherapies are available. Depression is typically treated with medication, psychotherapy, or a combination of both. Different patients appear to respond to different treatments. A patient who does not respond to one treatment may well respond to another (Crismon et al 1999; Depression Guideline Panel 1993b; Thase and Rush 1995).

At least 10% to 20% of all depressed patients do not have satisfactory sustained responses to present treatments.[1] Treatment resistance may increase with increasing numbers of episodes or increasing episode duration (Depression Guideline Panel 1993b; Thase and Rush 1995). About 100,000 patients annually, most of whom have treatment-resistant depression, receive a course of electro-

[1]Perhaps 1–4% of patients with major depressive episodes attain the level of treatment resistance required of this research sample.

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convulsive therapy (ECT; American Psychiatric Association Committee on ECT, in press; Olfson et al 1998).

Depression is now being recognized as a chronic or recurrent, disabling lifelong illness, rather than an isolated single episode from which lasting recovery can be expected. A well-tolerated treatment that provides both acute symptom relief and longer term benefits for this lifelong illness is needed (Glass 1999).

Vagus Nerve Stimulation (VNS), delivered by the NCP System (Cyberonics, Houston) for treatment-resistant partial-onset seizures in epilepsy, has been commercially available in Europe since 1994 and in the United States since 1997. The idea of using VNS as a treatment for clinical depression was initially based on 1) clinical observations of improved cognition and mood during studies of patients with epilepsy (Handforth et al 1998; Vagus Nerve Stimulation Study Group 1995) and 2) the fact that several anticonvulsant medications, including carbamazepine (Ballenger and Post 1978; Okuma et al 1973), gabapentin (Harden et al 1999a; Letterman and Markowitz 1999), lamotrigine (Calabrese et al 1999; Fatemi et al 1997), and valproate (Swann et al 1997), are used to treat mood disorders. Whereas decreased seizure frequency may have accounted for some mood improvement in patients with epilepsy who were treated with VNS, even some of those with little or no seizure improvement also reported substantial mood improvements (Harden et al 1999b; G. Elger et al, unpublished data, 1999). A detailed rationale for the use of VNS in the treatment of depression is provided in another article in this issue (George et al 2000).

Objectives

Our four-site study assessed the safety and efficacy of VNS in treating patients with treatment-resistant, chronic or recurrent, nonpsychotic, major depressive, bipolar I or bipolar II (both in the depressed phase) disorders. Vagus Nerve Stimulation was used with or without antidepressant medications. We aimed to 1) determine the degree and timing of antidepressant effects, if any, utilizing reliable, clinical assessments; 2) determine the safety and tolerability of VNS in this patient group; and 3) determine whether a randomized safety and efficacy study was warranted.

This open-label, nonrandomized, single-arm study of VNS was designed to enroll up to 45 patients to obtain a total of 30 treated patients who had implants under Investigational Device Exemptions (1980) approval from the United States Food and Drug Administration and appropriate institutional review board approvals.

Recruitment/Consent

All aspects of the protocol were managed in compliance with current United States regulations and international guidelines pertaining to good clinical practices.[2] The protocol and all amendments were reviewed and approved by each study site's institutional review board. Each patient signed a written informed consent.

We selected subjects who had prominent and definitive histories of treatment resistance, which in turn led to a sample with a very chronic prior history characterized by multiple treatment attempts in both the current and previous episodes, to ensure that the risk of an entirely untested intervention requiring surgery would be a logical and ethical consideration for every patient or participant.

Methods and Materials

Study Population

Patients had to have a DSM-IV diagnosis of major depressive disorder (MDD) or bipolar I or II disorder (American Psychiatric Association 1994). They had to be in a major depressive episode (MDE). The current MDE had to be $\geq$2 years in duration, or the patient (whether with unipolar or bipolar disorder) had to have $\geq$4 MDEs in his or her lifetime.

Patients also met the following inclusion/exclusion criteria. Men and women 18 to 70 years old were eligible, except for pregnant women and women not using acceptable birth control methods, which included abstinence. Patients had to 1) score $\geq$3 on the Antidepressant Treatment History Form (ATHF; Oquendo et al 1999; Prudic et al 1990, 1996; Sackeim et al 1990), indicating that they had failed on $\geq$2 antidepressant medication treatments from different medication classes during the current MDE[3]; 2) have had no substantial clinical improvement with psychotherapy (at least 6 weeks); 3) score $\geq$20 on the 28-item Hamilton Depression Rating Scale[4] ($HDRS_{28}$; Hamilton 1960, 1967; Williams 1988); 4) score $\leq$50 on the Global Assessment of Function (GAF; American Psychiatric Association 1994); and 5) have an IQ $\geq$70 (investigator judgment). Those with bipolar disorder had to have either resistance, intolerance, *or* a medical contraindication to lithium.

Patients were excluded if they had 1) atypical or psychotic features in the current MDE; 2) a history of schizophrenia, schizoaffective disorder, or other non–mood disorder psychosis; 3) rapid-cycling bipolar disorder; or 4) a current secondary diagnosis (or signs) of delirium, dementia, amnesia, or other cognitive disorder (by DSM-IV). Also excluded were patients with clinically significant, current suicidal intent and those with certain risks related to surgical implantation and treatment.

[2]The protocol was conducted in compliance with the *Investigational Device Exemptions Manual* (1996; IDE Number G980099) and was monitored by Cyberonics, Inc.

[3]Medication classes included selective serotonin reuptake inhibitors, heterocyclic antidepressants, monoamine oxidase inhibitors, other antidepressant medications, lithium, electroconvulsive therapy, and anticonvulsants.

[4]The 28-item Hamilton Depression Rating Scale includes atypical symptom features (anergia, hypersomnia, increased appetite, and rejection sensitivity).

Study Overview

All patients followed the same treatment schedule. Following written informed consent, patients completed a "baseline period" (up to 4 weeks) preimplantation during which clinical assessments were performed on two separate occasions. To qualify for implantation, patients had to score ≥20 on the $HDRS_{28}$ during both baseline visits. Patients on medications had to maintain a stable medication regimen for at least 4 weeks prior to the initial baseline visit.[5]

For 2 weeks following implantation, (single-blind "recovery period"), the NCP System remained off to allow for surgical recovery. Patients were told that "stimulation may or may not be turned on immediately after surgery." Clinical assessments were performed weekly. Further, during this recovery period, patients had to score ≥18 on the $HDRS_{28}$ for two consecutive visits (7 and 14 days postimplantation) before initiating stimulation.[6]

At the end of the recovery period, the NCP System was turned on and the output current (mA setting) was progressively increased to the maximum, comfortably tolerated level over the next 2 weeks ("stimulation adjustment period"), with clinical assessments performed weekly.

At 4 weeks postimplantation (i.e., after 2 weeks of VNS), stimulation parameters were set and left unchanged for the remaining 8 weeks. (A decrease in stimulation parameters was permitted if intolerable side effects developed, but no patient required decreased stimulation.) Patients were seen weekly for the next 2 weeks and then every other week for another 6 weeks. This "fixed-dose stimulation period" lasted 8 weeks; the total duration of stimulation was 10 weeks.

After completion of the acute study, patients were allowed to continue receiving VNS. All patients are being observed clinically at least 9 months after the acute study exit and for at least 12 months following implantation.[7] During this long-term "follow-up period," either NCP stimulation parameters or concomitant medications may be changed based on investigator or primary physician judgment. As such, follow-up data provide descriptive information as to longer term outcomes.

Treatment

The NCP System implantation technique and the programming sequence used in this study were identical to those used in the studies of treatment-resistant epilepsy. The NCP System includes an implantable and multiprogrammable pulse generator that delivers electrical signals to the left vagus nerve (10th cranial nerve) via the bipolar lead. The pulse generator is programmed via a programming wand attached to a computer, which sets or adjusts stimulation parameters. Additional information about the NCP System has been provided in another article in this issue (George et al 2000).

After completion of the 2-week, postimplantation, single-blind "recovery period," the device was turned on with initial stimulation parameters of 0.25 mA, 20 or 30 Hz,[8] and 500 μsec, with stimulation on for 30 sec every 5 min. At this visit, the output current was increased gradually (in 0.25-mA increments) to allow accommodation to the stimulation until a comfortable tolerance level was reached. After a comfortably tolerated output current was attained, the patient left the clinic at these settings.

Additional increases (in 0.25-mA steps) in output current were made anytime during the "stimulation adjustment period" over the next 2 weeks. Stimulation parameter settings were determined based on patient tolerance. Investigators were allowed by protocol a range of frequency (e.g., 20–30 Hz), pulse width (e.g., 250–500 μsec), and on/off cycle parameters (e.g., off 3 or 5 min). In general, the stimulation parameters commonly used for epilepsy were used in this study.

Concomitant Therapy

No patient received concomitant ECT, investigational drugs, or treatment with another investigational device during the study. Patients were allowed (but not required) to take antidepressant and/or mood stabilizer medications, as long as the same doses and same medication types were maintained during the baseline period and for 12 weeks following implantation. Medications could be decreased, but not increased, during the acute study. Lorazepam (up to 3 mg/day) was allowed for anxiety and/or insomnia as needed. Other medications (i.e., antibiotics, decongestants, analgesics, and over-the-counter medications) were allowed (though investigators made all reasonable attempts to either limit or discourage over-the-counter medications during the study). Concomitant medications were recorded at each visit.

Evaluations and Outcome Measurements

Baseline evaluations included a medical and psychiatric history, physical and neurologic exams, and presurgical laboratory tests. Efficacy and safety data were gathered at the two baseline visits and at weeks 1 and 2 (recovery period), 3 and 4 (stimulation adjustment period), and 5, 6, 8, 10, and 12 (fixed-dose stimulation period) after implantation. Clinical assessments of depressive symptoms included the $HDRS_{28}$ and the 10-item Montgomery–Åsberg Depression Rating Scale (MADRS; Montgomery and Åsberg 1979). Manic/hypomanic symptoms were rated by the Young Mania Rating Scale (Young et al 1978). Overall status and response were gauged by the Clinical Global Impressions—Improvement (CGI-I) and Severity (CGI-S) indices (Guy 1976) and the GAF (American Psychiatric Association 1994). Functional outcomes were also assessed using the Medical Outcomes Study (MOS) 36-item short form (SF-36; Ware and Sherbourne 1992).

Stimulation parameter settings were documented at each visit (and at any additional visit if stimulation parameters were

[5]Patients were allowed to continue stable medication regimen(s) rather than become medication free because 1) the medication(s) had provided some relief that could be lost if discontinued; 2) almost all patients, we believe, would have declined to stop taking even these modestly beneficial treatment(s); and 3) the medication discontinuation symptoms and possible significant clinical worsening were avoided using this scheme.

[6]If patients had scored less than 18, they would have had an extended visit and been observed weekly until the 28-item Hamilton Depression Rating Scale score was 18 or more, at which time the regular visit schedule would have been reinitiated. No patient required extended visits.

[7]After 1 year, patients can still continue to receive treatment.

[8]Standard frequency was changed from 30 Hz to 20 Hz in a protocol amendment—a change not expected to affect clinical outcome.

Table 1. Clinical and Demographic Features (n = 30)

	%	Mean ± SD	Median	Range
Female	67			
Caucasian	100			
MDD, recurrent	50			
MDD, single episode	20			
Bipolar I disorder	13			
Bipolar II disorder	17			
Current MDE of ≥2 years	70			
Age (years)		47.5 ± 7.5	47.9	28.6–63.1
Length of current MDE (years)		10.3 ± 12.5	4.7	0.3–49.5
Age at onset of current MDE (years)		37.2 ± 12.4	40.4	8.0–57.6
Length of illness (years)		19.3 ± 13.1	19.6	0.3–49.5

MDD, major depressive disorder; MDE, major depressive episode.

adjusted). During the fixed-dose stimulation period, parameter settings were confirmed by interrogating the pulse generator at each visit. Adverse events and concomitant medications were coded using the *Coding Symbols for Thesaurus of Adverse Reaction Terms* (1995) and *World Health Organization Drug Dictionary* (1999), respectively. Holter monitoring data for at least 12 hours were collected at baseline (between baseline visits 1 and 2) and at the end of acute study (12 weeks postimplantation).

Data Management and Analysis

Cyberonics conducted routine clinical monitoring visits at all sites. Data were entered, verified, and analyzed using procedures that ensured the quality of the data and results. Response was defined *a priori* as a ≥50% reduction at exit in the mean $HDRS_{28}$ score obtained at the two baseline (preimplantation) visits (or, for secondary analyses, a ≥50% reduction in baseline MADRS or a CGI-I score of 1 or 2).

Results

Enrollment

A total of 38 patients were enrolled, 30 of whom had implants (Dallas, 14; Charleston, 7; Houston, 6; New York, 3). Of the eight who enrolled but did not have implants, four withdrew consent, one responded to changed medications, and three no longer met the inclusion/exclusion criteria. This report summarizes findings for the 30 patients with implants, all of whom completed the acute study, and the available postacute study (long-term follow-up) outcomes.

Sample Features

Table 1 presents the clinical and demographic features of the sample. The patient population was 67% female. Most (70%) had MDD, and nearly 50% of those with MDD had recurrent MDD. The median length of the current MDE was 4.7 years. Over two thirds (70%) of the patients had been in the current MDE for ≥2 years.

Table 2. Number and Percent of Patients Taking Antidepressant Treatments (n = 30)

	Lifetime	Current episode	Acute study
Treatment	n (%)	n (%)	n (%)
Selective serotonin reuptake inhibitors (total)	30 (100)	29 (97)	13 (43)
1	4 (13)	8 (27)	11 (37)
2	7 (23)	8 (27)	1 (3)
3	7 (23)	5 (17)	1 (3)
4	8 (27)	4 (13)	0 (0)
5	4 (13)	4 (13)	0 (0)
Heterocyclics/tricyclics (total)	25 (83)	20 (67)	4 (13)
1	10 (33)	9 (30)	4 (13)
2	2 (7)	2 (7)	0 (0)
3	5 (17)	5 (17)	0 (0)
4	3 (10)	3 (10)	0 (0)
≥5	5 (17)	1 (3)	0 (0)
Bupropion	24 (80)	21 (70)	3 (10)
Venlafaxine	23 (77)	22 (73)	7 (23)
Lithium	23 (77)	19 (63)	4 (13)
Electroconvulsive therapy	19 (63)	17 (57)	0 (0)
Mirtazapine	19 (63)	17 (57)	3 (10)
Monoamine oxidase inhibitors (total)	18 (60)	14 (47)	0 (0)
1	8 (27)	5 (17)	0 (0)
2	8 (27)	7 (23)	0 (0)
3	2 (7)	2 (7)	0 (0)
Trazodone[a]	13 (43)	8 (27)	2 (7)
Nefazodone	15 (50)	15 (50)	4 (13)

[a] "Counted" only if doses exceeded 200 mg/day or patient stated it was not used solely as a hypnotic.

Tables 2 and 3 present the treatment histories (lifetime, during the current episode, and during VNS) of all patients. Over their lifetimes, patients averaged 18.4 ± 7.2 (range = 6–38) antidepressant and mood disorder treatments, of which 10.3 ± 3.7 (range = 4–18) were antidepressant medication trials. Altogether, 63% had received ECT in their lifetime, whereas 57% had received ECT during the current MDE. Ten (33%) had received ECT within 2 years of study entry. Of the 19 patients who had *ever* received ECT, seven had no response (no or minimal symptom reduction), three had partial responses (only modest symptom reduction), eight had transient responses (substantial symptom reduction lasting <2 months), and one had a sustained response.

All patients met or exceeded eligibility criteria by failing at least two robust treatment trials in the current MDE according to the ATHF. To qualify, the agent had to be used at doses with established efficacy for a sufficient period (e.g., at least 4 weeks) to establish that the agent was ineffective. During the current MDE, 30% had failed

Table 3. Number and Percent of Patients Taking Other Mood Disorder Treatments ($n = 30$)

	Lifetime	Current episode	Acute Study[a]
Treatment	n (%)	n (%)	n (%)
Carbamazepine, lamotragine, valproate (total)	20 (67)	19 (63)	5 (17)
1	7 (23)	7 (23)	5 (17)
2	8 (27)	7 (23)	0 (0)
3	5 (17)	5 (17)	0 (0)
Other anticonvulsants (total)	21 (70)	21 (70)	11 (37)
1	13 (43)	13 (43)	10 (33)
2	5 (17)	5 (17)	0 (0)
≥3	3 (10)	3 (10)	1 (3)
Atypical antipsychotics (total)	22 (73)	22 (73)	10 (33)
1	8 (27)	8 (27)	10 (33)
2	8 (27)	8 (27)	0 (0)
3	6 (20)	6 (20)	0 (0)
Stimulants (total)	16 (53)	15 (50)	7 (23)
1	7 (23)	7 (23)	7 (23)
2	7 (23)	7 (23)	0 (0)
3	2 (7)	1 (3)	0 (0)
Repeated transcranial magnetic stimulation	3 (10)	3 (10)	0 (0)
Phototherapy	2 (7)	2 (7)	1 (3)
Thyroid augmentation	13 (43)	13 (43)	1 (3)
Nonatypical antipsychotics (total)	13 (43)	9 (30)	3 (10)
1	7 (23)	5 (17)	3 (10)
2	3 (10)	3 (10)	0 (0)
3	3 (10)	1 (3)	0 (0)
Anxiolytics (total)	26 (87)	25 (83)	15 (50)
1	9 (30)	11 (37)	13 (43)
2	10 (33)	9 (30)	1 (3)
3	6 (20)	4 (13)	1 (3)
4	1 (3)	1 (3)	0 (0)
Other[b]	4 (13)	4 (13)	1 (3)

[a]Treatments received during the period from implantation to acute study exit.
[b]Other treatments included ω3 fatty acids, flax seed oil, etc.

two treatments, 7% had failed three, 20% had failed four, and 43% had failed five or more well-documented treatments that met ATHF criteria. Tables 2 and 3 reveal, in fact, that many more treatment attempts were made, often in combinations, for the current MDE. As a group, the patients were remarkably treatment resistant—resulting in prolonged, severe, and disabling illness.

Concomitant Treatments during the Acute Study

Patients were taking from zero ($n = 5$) to four (median = 1) antidepressant medications while receiving VNS, during the acute study. They were also taking a mean of 3.5 ± 1.7 (median = 4, range = 1–8) other mood disorder treatments while receiving VNS, during the acute study.

To determine if the overall strength of the antidepressant treatment regimen received concomitantly during the acute study was a prognostic indicator of treatment response, a modification of the Antidepressant Resistance Rating (ARR) based on the ATHF ratings was used to calculate the Total Strength of Treatment (TST) score. The individual ATHF ratings for each mood disorder treatment that a patient was taking during the acute study were added together to obtain a TST score. For example, if a patient was taking 525 mg venlafaxine (ARR = 4), 6 mg clonazepam (ARR = 0), and 2 mg risperidone (ARR = 1) during the acute study, then the TST score would equal 5. Medications (as circumstances require) were included in the calculation of the TST, if they were rated at a strength >1 on the ARR. Patients had a mean TST score of 5.8 while receiving VNS during the acute study.

VNS Treatment

All 30 patients had the stimulation parameters set at 500-μsec pulse width and 20- ($n = 25$) or 30-Hz ($n = 5$) frequency for 30 sec on and 5 min off, except for one who received a 250-μsec pulse width and for three others who received stimulation for 30 sec on and 3 min off. Output currents ranged from 0.25 to 3.0 mA depending on patient tolerance (median 0.75 mA).[9] Once the stimulation parameters were set at the end of the 2-week stimulation adjustment period, no patient required stimulation parameter adjustments during the fixed-dose stimulation period. No device malfunctions or complications were encountered.

Symptomatic Outcomes

Figure 1 presents the $HDRS_{28}$ total score at the exit visit for each patient and the percent reduction in the average (two visits) baseline $HDRS_{28}$ in relation to the diagnosis for each patient ($n = 30$). Overall, a 40% response rate was found using a ≥50% reduction in the baseline $HDRS_{28}$ total score to define response.

Table 5 presents the mean scores for each major clinical outcome variable at baseline, recovery, and acute study exit. At exit, according to the CGI-I, 3% were minimally worse, 27% were unchanged, 30% were minimally improved, 20% were much improved, and 20% were very much improved at acute study exit. When complete response is defined as exit $HDRS_{28} \leq 10$, 17% of patients responded completely. Global Assessment of Function scores improved from 40.6 at baseline to 61.9 at acute study exit.

[9]There was no experimentation with alternative stimulation parameters to optimize efficacy during the stimulation adjustment period, since onset of improvement in depressive symptoms, when it occurred, typically took longer than the 2-week stimulation adjustment period permitted by the protocol.

Table 4. Number and Percent of Patients Reporting Adverse Events Occurring in ≥7% of Patients (n = 30)

			Stimulation related		
		Surgery related	Possible	Probable	Definite
Body system	COSTART term	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Body as a whole	Incision site pain	9 (30)	0 (0)	0 (0)	0 (0)
	Headache	2 (7)	5 (17)	0 (0)	2 (7)
	Pain	2 (7)	0 (0)	2 (7)	3 (10)
	Chest pain	1 (3)	3 (10)	0 (0)	1 (3)
	Neck pain	0 (0)	1 (3)	2 (7)	2 (7)
	Infection	2 (7)	0 (0)	0 (0)	0 (0)
Respiratory	Voice alteration	2 (7)	1 (3)	3 (10)	12 (40)
	Pharyngitis	1 (3)	2 (7)	4 (13)	1 (3)
	Dyspnea	1 (3)	2 (7)	3 (10)	1 (3)
	Coughing	0 (0)	0 (0)	1 (3)	3 (10)
Digestive	Dysphagia	1 (3)	0 (0)	1 (3)	3 (10)
	Dyspepsia	2 (7)	0 (0)	1 (3)	0 (0)
	Nausea	1 (3)	2 (7)	0 (0)	0 (0)
Nervous	Dizziness	0 (0)	3 (10)	0 (0)	0 (0)
	Hypertonia	1 (3)	0 (0)	0 (0)	2 (7)
	Twitching	0 (0)	0 (0)	2 (7)	0 (0)
Skin and appendages	Rash	1 (3)	2 (7)	0 (0)	0 (0)
Metabolic/nutritional disorders	Abnormal healing	3 (10)	0 (0)	0 (0)	0 (0)
	Edema	2 (7)	0 (0)	0 (0)	0 (0)
Special senses	Ear pain	0 (0)	2 (7)	0 (0)	0 (0)

COSTART, *Coding Symbols for Thesaurus of Adverse Reaction Terms* (1995).

Figure 2 presents the mean $HDRS_{28}$ scores at each study visit for the whole group (n = 30) and for responders (n = 12) and nonresponders (n = 18; defined by the threshold of >50% reduction in the baseline $HDRS_{28}$ total). Separately, for responders (n = 12), early effects (i.e., during VNS dose adjustment) are suggested, but more than half of the total reduction from 39.1 (average at baseline) to 12.3 (average at exit) for responders occurred over 6 of the 8 weeks of fixed-dose VNS. No patient responded during the 2-week, postimplantation (no stimulation), single-blind recovery period, using the $HDRS_{28}$ to define response (n = 12), with six of the 12 patients (50%) who

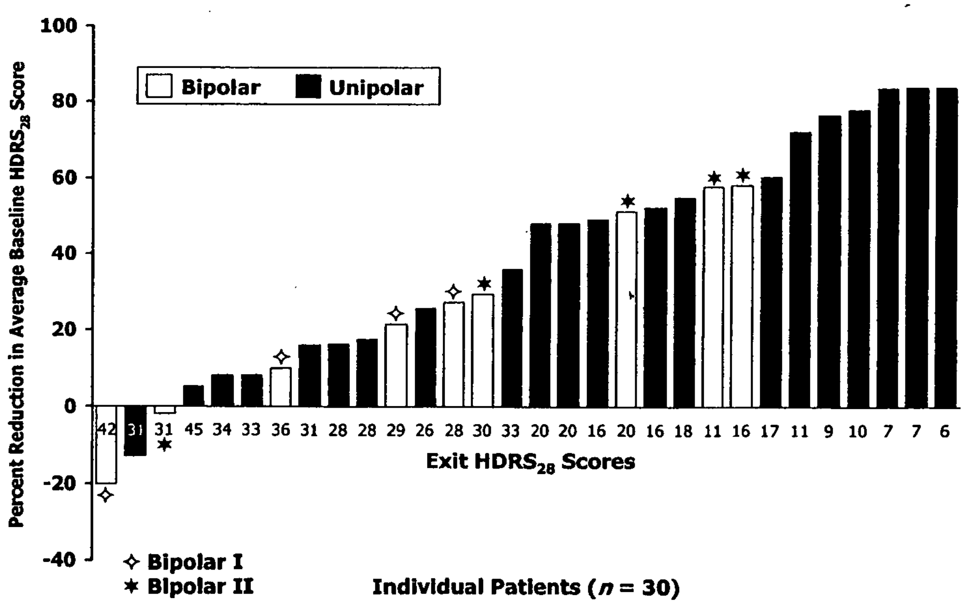

Figure 1. Response by diagnosis (unipolar and bipolar) and exit 28-item Hamilton Depression Rating Scale ($HDRS_{28}$) score.

Table 5. Major Clinical Outcomes

Rating Scale	Baseline period[a]	Recovery period[b]	Acute study exit
$HDRS_{28}$	38.0 ± 5.5	36.6 ± 6.6	23.0 ± 10.8
MADRS	33.8 ± 5.6	32.5 ± 7.1	20.1 ± 12.2
CGI-I[c]	NA	0%	40.0%
CGI-S	5.3 ± 0.7	5.1 ± 0.7	3.7 ± 1.4
GAF	40.6 ± 6.8	43.2 ± 9.8	61.9 ± 16.8
YMRS	2.3 ± 1.3	2.2 ± 2.1	1.9 ± 3.4

Results are means ± SDs or %. $HDRS_{28}$, 28-item Hamilton Depression Rating Scale; MADRS, Montgomery–Åsberg Depression Rating Scale; CGI-I, Clinical Global Impressions—Improvement; CGI-S, Clinical Global Impressions—Severity of Illness; GAF, Global Assessment of Functioning; YMRS, Young Mania Rating Scale.

[a]Calculated as the average of visits 1 and 2.

[b]Calculated as the average of visits 4 and 5.

[c]Reported as the percentage of patients with a score of 1 or 2.

ultimately responded doing so by week 5 following implantation.

Effect on Function

Table 6 presents the MOS SF-36 overall and subscale results (baseline to exit) for all patients, as well as separately for responders and nonresponders (defined by ≥50% reduction in baseline $HDRS_{28}$). Note that baseline function was remarkably low (e.g., role emotional = 6.9, role function = 41.4, vitality = 9.0, social function = 22.0, etc.). Response (by $HDRS_{28}$) was associated with highly clinically significant increases in the mental component, role function, vitality, social function, role emotional function, and mental health. Nonresponders did not change (save for a statistically significant increase in social function of 10 points). Of the 12 responders, 25% achieved exit role emotional ratings that equaled or exceeded population norms, indicating that these patients achieved normal functioning.

Which Patients Respond to VNS?

A logistic regression analysis was conducted using $HDRS_{28}$ response and the following prognostic factors: $HDRS_{28}$ total baseline score, diagnosis (major depressive or bipolar disorder), length of index MDE, total length of illness, age, prior ECT response, VNS stimulation output current, and TST score. A univariate model indicated that the only potentially significant factors concerned prior ECT response and VNS stimulation output current (mA); however, the relationship between ECT response and VNS response did not reach statistical significance (p = .10) in a multivariate model that included both ECT response and output current. Lower levels of VNS stimulation output current were associated with better treatment response (p = .07) in the same multivariate model.

Of seven patients not responding at all (either partially or transiently) to ECT, only one responded to VNS. Within the five categories of ECT response, the logistic regression odds ratio was strongest when patients who had completely failed to respond acutely to ECT were compared with all other patients (i.e., those who never had ECT combined with those with transient or partial responses).

Adverse Events

No patient discontinued the acute study due to adverse events. Reported adverse events were similar to those in

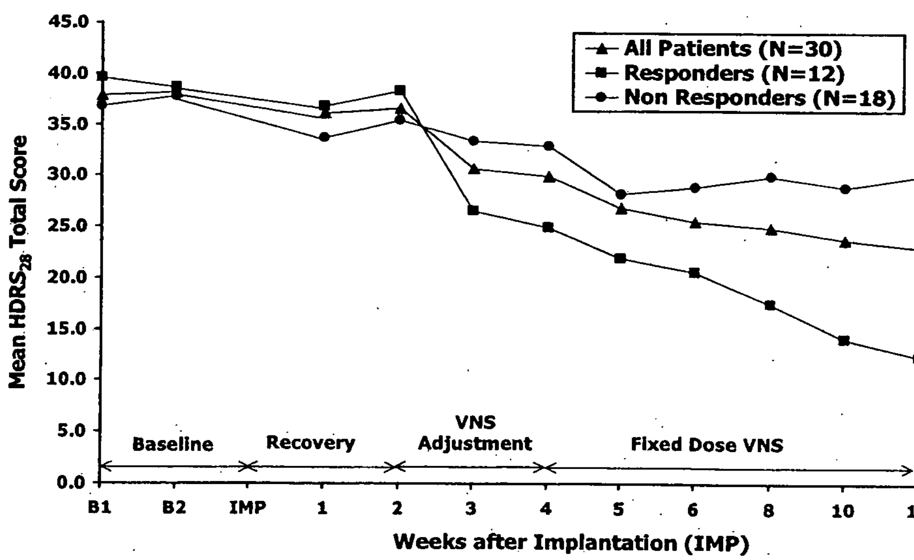

Figure 2. Mean 28-item Hamilton Depression Rating Scale ($HDRS_{28}$) score during acute study.

Table 6. Mean Scores on the Medical Outcomes Study 36-Item Short Form

Variable	Overall (n = 29)		Responders (n = 12)		Nonresponders (n = 17)	
	Baseline	Exit	Baseline	Exit	Baseline	Exit
Mental component[a]	18.8	29.5[b]	17.2	39.9[b]	19.9	22.5
Physical component[a]	44.6	44.1	46.2	46.0	44.1	42.7
Subscales						
Physical function	55.0	61.1[b]	56.7	68.0	55.3	56.2
Role function	41.4	48.3	31.3	66.7[b]	51.4	35.3
Pain index	51.9	54.8	56.4	61.8	47.7	49.8
Health perceptions[a]	49.4	54.0	56.3	63.1	46.5	47.6
Vitality improvements	9.0	25.3[b]	7.1	43.3[b]	12.5	14.7
Social function	22.0	42.7[b]	24.0	61.5[b]	19.4	29.4[b]
Role emotional	6.9	26.4	5.6	47.2[b]	11.1	11.8
Mental health	24.7	42.0[b]	20.7	60.9[b]	26.2	28.7

[a]One patient did not fully complete the questionnaire.
[b]Statistically significant percent change from baseline using $p < .05$ and paired t test.

previous studies of epilepsy (Table 4). Some adverse events were related to implantation and stimulation, with most of the treatment-related adverse events being stimulation related. Nine patients (30%) reported pain at the incision site, which typically dissipated over 1 to 2 weeks. The most common events reported as possibly, probably, or definitely related to stimulation were hoarseness (60%), throat pain (27%), headache (30%), shortness of breath (23%), general pain (23%), and neck pain (17%). All events had been reported with VNS in previous epilepsy studies (Handforth et al 1998; Vagus Nerve Stimulation Study Group 1995)—although headaches were not as commonly associated with stimulation in the epilepsy trials. In general, stimulation-related adverse events (including hoarseness and throat pain) were mild and well tolerated, and they occurred only when stimulation was on. One patient developed hypomania, which subsided with stimulation reduction.

Additionally, three patients (10%) reported abnormal wound healing, which involved a longer time for implant incisions to heal. All patients' wounds healed without significant intervention. These events all occurred at one site; the surgeon has since modified his incision closure technique. After implantation, two patients (7%) at one site experienced rashes, which eventually subsided.

Six clinically significant adverse events occurred, five during the acute study and one during the long-term follow-up. One event, infection, was related to implantation. Two separate events of leg pain reported by one patient may have been related to implantation. Two events (agitation/panic during the acute study and agitation/irritability/dysphoria in the long-term follow-up) were reported as possibly related to stimulation. One event of worsened depression due to benzodiazepine withdrawal was reported as not related to stimulation.

Safety Testing and Post–Acute Study Follow-Up

Twenty-four-hour Holter monitor results revealed no significant cardiac changes when comparing baseline with acute study exit recordings. Nearly all patients (29/30, 97%) have continued to receive VNS treatment after exiting the acute study. One patient had the NCP generator explanted after 10.8 months of follow-up, due to an inability to sustain antidepressant effects at levels of stimulation that were comfortable. To date, all 10 patients who responded acutely and for whom follow-up data are available have maintained response (Table 7), though two patients experienced a transient worsening on one follow-up occasion. Recall that changes to stimulation parameters and mood-stabilizing medications were both permitted and made during follow-up. At their most recent follow-up visits, seven of these 10 acute study responders demonstrated a complete response ($HDRS_{28} \leq 10$).

Discussion

This is the first report of VNS in adult outpatients with severe, nonpsychotic, treatment-resistant MDEs. Response rates of 40% (by $HDRS_{28}$ and by CGI) or 50% (MADRS), as well as the 17% complete response (remission) rate (exit $HDRS_{28} \leq 10$), suggest efficacy in this very treatment-resistant population. Responses occurred between 1 and 10 weeks following the initiation of stimulation.

To date, all of the 10 responders for whom we have follow-up visit data after acute study exit have basically sustained the response status over the 4–9 months following implantation. Additionally, as of the most recent follow-up visit, seven of these 10 acute-phase responders have attained or remained in remission ($HDRS_{28} \leq 10$). No significant correlates of VNS response were found, though a larger sample is needed to evaluate both prior

Table 7. Summary of the 28-Item Hamilton Depression Rating Scale Scores during Long-Term Follow-Up for Responders (n = 10)

Baseline average	Acute exit	Follow-up (months) 1	2	3	4	5	6
41	20 (51)	—	13 (68)				
43	7 (84)	—	—	4 (91)	—	—	1 (98)
40	18 (55)	—	—	16 (60)			
38.5	9 (77)	—	—	2 (95)	9 (77)		
37.5	6 (84)	—	—	14 (63)	8 (79)		
45.5	10 (78)	—	—	26 (43)	5 (89)		
43	17 (61)	21 (51)					
33.5	16 (52)	8 (76)	2 (94)				
26	11 (58)	24 (8)	6 (77)				
43.5	7 (84)	1 (98)					

Percent improvement from baseline is shown in parentheses. Dash (—) indicates that visit was not performed.

ECT response and output current (mA) settings as potential predictors. Studies of VNS in epilepsy have found no relationship between response and output current. Failure to respond at all (i.e., not even partially or transiently) to prior ECT may be a possible predictor of nonresponse to VNS, as might higher stimulation currents. A larger sample is needed.

Adverse events were no different than those previously noted with VNS in patients with epilepsy. No patients discontinued VNS due to adverse events. Most typically occurred only while stimulation was on. No serious, unanticipated adverse events occurred during the study. One patient developed hypomania that resolved with a reduction in stimulation.

Given the small sample size, these findings are preliminary. Furthermore, ratings were not blinded. However, symptomatic responses were accompanied by very substantial improvements in overall function based on the MOS SF-36, which corroborates the symptomatic ratings.

In addition, there was no control group. Without a randomized, sham-control group, one cannot draw definite conclusions about effectiveness in this patient population. However, the severe, chronic, disabling, and treatment-resistant nature of the depressive episodes in this patient sample suggests that only 5–10% of these patients would have been expected to improve spontaneously or to respond to any established treatment during the 3 months following implantation (Sackeim et al 1993; Thase and Rush 1995). The response rate that was found (i.e., 40%) substantially exceeds these expectations.

Although neither spontaneous improvement nor a placebo response can be absolutely excluded without a control group, several points argue against such effects in this study. First, no patient responded in the 2-week, postimplantation, single-blind recovery period. In fact, no change in $HDRS_{28}$ average scores between baseline (preimplantation) and recovery was found. This finding suggests that the responses obtained were due neither to the passage of time nor to the nonspecific effects of the treatment process. Second, the nature of the sample itself, with prolonged, index MDEs aggressively treated before study entry, argues against nonspecific effects causing these results.

Third, the follow-up data suggest that patients who initially improved retained that improvement after acute study exit. A pattern of sustained benefit is unlikely to be a "placebo response" (Quitkin et al 1991; Shea et al 1992; Thase and Rush 1995). Underlying chronic depression and three or more previous affective episodes predict a statistically significant increase in the rate of relapse (Keller et al 1982), so significant relapse would be expected for this population. Since all responders to date have sustained the acute improvements in the longer term, VNS appears to provide ongoing benefit for those who do respond. In fact, relapse rates of 20–30% have commonly been reported in patients with far less severe, nonresistant major depression while in continuation or maintenance medication treatment studies (Doogan and Caillard 1992; Feiger et al 1999; Montgomery et al 1988, 1993; Montgomery and Dunbar 1993; Versiani et al 1999). Relapse rates were even higher (up to 50%) among patients who receive ECT (Sackeim 1994; Sackeim et al 1990; Shapira et al 1995). For patients who are medication resistant but who respond to ECT, relapse rates are even higher than for those who are less medication resistant (Devanand et al 1991; Prudic et al 1990; Sackeim et al 1990).

Other findings suggestive of antidepressant activity include 1) the onset of hypomania in one patient, 2) the fact that two of the five (40%) patients taking no antidepressants responded (equivalent to the overall response rate), and 3) that the trend suggesting lower rather than higher current settings may be associated with a better response (nonblinded investigators would be biased toward expecting higher settings to be more effective).

This study of VNS delivered by the NCP System in the treatment of patients with severe treatment-resistant depression encourages further investigation of the safety and efficacy of VNS in treatment-resistant depression, especially because the acute benefits of VNS seem to persist. Further studies are needed to determine if, as in epilepsy, benefits beyond those obtained acutely accrue over time.

Future studies should likely give consideration to the following questions:

1. Can nonresponders to VNS during the acute study become responders after long-term treatment with changes in stimulation parameters?
2. Does VNS continue to provide ongoing, sustained symptom relief over months or years following acute phase response?
3. Are there "predictors" or "correlates" of response or of time to response?
4. Can medication amounts or types be reduced or eliminated once a stable, sustained response to VNS is obtained?
5. Where does VNS fit into treatment algorithms for managing major depressive or bipolar disorder?

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Vagus Nerve Stimulation: A New Tool for Brain Research and Therapy*

Mark S. George, Harold A. Sackeim, A. John Rush, Lauren B. Marangell, Ziad Nahas, Mustafa M. Husain, Sarah Lisanby, Tal Burt, Juliet Goldman, and James C. Ballenger

Biological psychiatry has a long history of using somatic therapies to treat neuropsychiatric illnesses and to understand brain function. These methods have included neurosurgery, electroconvulsive therapy, and, most recently, transcranial magnetic stimulation. Fourteen years ago researchers discovered that intermittent electrical stimulation of the vagus nerve produces inhibition of neural processes, which can alter brain electrical activity and terminate seizures in dogs. Since then, approximately 6000 people worldwide have received vagus nerve stimulation for treatment-resistant epilepsy. We review the neurobiology and anatomy of the vagus nerve and provide an overview of the vagus nerve stimulation technique. We also describe the safety and potential utility of vagus nerve stimulation as a neuroscience research tool and as a putative treatment for psychiatric conditions. Vagus nerve stimulation appears to be a promising new somatic intervention that may improve our understanding of brain function and has promise in the treatment of neuropsychiatric disorders. Biol Psychiatry 2000;47:287–295 *© 2000 Society of Biological Psychiatry*

Key Words: Vagus nerve, locus ceruleus, antidepressant, brain stimulation, depression

*See accompanying Editorial, in this issue.

Historical Introduction

An Overview of Somatic Interventions (Table 1)

Since its inception, biological psychiatry has embraced the use of somatic interventions for brain research and clinical treatment. Indeed, many of the founders of the 55-year-old Society of Biological Psychiatry were researchers who were interested in understanding the mechanisms of action of electroconvulsive therapy (ECT).

Although the revolution in neuropsychopharmacology over the last 40 years has captured much interest, recent advances in somatic interventions (e.g., physical, nonpharmacological) are causing a resurgence of interest in other methods that directly and, in some cases (transcranial magnetic stimulation [TMS]), noninvasively affect brain function. The field of ECT continues to advance, with recent demonstrations of the need for dosage titration (Sackeim et al 1987b) and regional specificity of ECT effects (Sackeim et al 1987a, 1993) and even the recent production of ECT-like seizures using magnetic instead of electrical currents (Lisanby et al 1999). There has also been considerable interest in TMS (without seizure production), which holds promise as a research tool with potential clinical applications (George and Belmaker 1999; George et al 1999).

The most anatomically discrete and most invasive currently employed method of stimulating deep brain structures is deep brain stimulation (DBS), in which a thin electrode is inserted directly into the brain and different currents are applied at varying depths until the desired effects are found. Recently, high-frequency (>80 Hz) electrical stimulation of the middle thalamus or subthalamic nucleus has been found to be effective in Parkinson's disease (Damier 1998; Limousin et al 1998). Whereas DBS has the advantage over brain surgery (pallidotomy) of being reversible, it has significant morbidity and mortality associated with the implant procedure. Although this technique has not been used to treat major depression, mood effects of the stimulation have been reported. In one Parkinson's disease patient who had never suffered from depression in her life, the testing of the stimulation caused the acute onset of tearfulness, sadness, and despair. These symptoms remitted immediately when the surgeon moved the stimulator away from the substantia nigra, directly below the subthalamic nucleus (Bejjani et al 1999). Parkinson's disease researchers lead the neuropsychiatric field in terms of understanding a dis-

From the Departments of Psychiatry (MSG, ZN, JG, JCB), Radiology (MSG), and Neurology (MSG), Medical University of South Carolina, and the Ralph H. Johnson Veterans Hospital (MSG), Charleston, South Carolina; the Department of Biological Psychiatry, New York State Psychiatric Institute (HAS, SL, TB) and the Departments of Psychiatry (HAS, SL, TB) and Radiology (HAS), College of Physicians and Surgeons, Columbia University, New York, New York; and the Department of Psychiatry, University of Texas Southwestern Medical Center, Dallas (AJR, MMH) and the Department of Psychiatry, Baylor College of Medicine, Houston (LBM), Texas.
Address reprint requests to Dr. Mark S. George, Radiology Department, Medical University of South Carolina, 171 Ashley Avenue, Charleston, SC 29425.
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Table 1. Current and Potential Somatic Interventions for the Treatment of Depression

Somatic intervention	Regionally specific?	Clinically applicable?	Invasive?
Electroconvulsive therapy	++ (+++ if induced by magnets	++++	++ (anesthesia, generalized seizure)
Transcranial electrical stimulation	+	++	+ (scalp irritation)
Transcranial magnetic stimulation	++++	+++ (clinical trials underway)	+ (painful at high intensities)
Vagal nerve stimulation	++ (discrete brainstem nuclei initially, unclear if different parameters selectively involve other brain regions)	+++ (on the market for epilepsy, clinical trials in depression [see Rush et al 2000])	+++ (surgery for generator implant)
Deep brain stimulation	++++	+++ (approved in the United States for treatment in movement disorders, pain syndromes; no work in depression yet)	++++ (brain surgery)

+, a little; ++++, a lot.

ease's involved pathologic circuitry. Thus it is natural for DBS to be used first in Parkinson's disease. However, as the neuroanatomy of other neuropsychiatric disorders (mood, anxiety, and psychosis) becomes better understood, it is conceivable that DBS may be helpful to otherwise treatment-resistant patients, although to date DBS has only been shown to cause depression symptoms rather than relieve them.

The History of Vagus Nerve Stimulation (VNS)

Another, less invasive means of directly affecting central function is to stimulate the cranial nerves that are direct extensions of the brain. For years, scientists have been interested in whether and how autonomic functions modulate activity in the limbic system and higher cortex. Numerous studies have identified extensive projections of the vagus nerve via its sensory afferent connections in the nucleus tractus solitarius (NTS) to many brain areas (Bailey and Bremer 1938; Dell and Olson 1951; Maclean 1990). As early as 1938, Bailey and Bremer reported that VNS in the cat elicited synchronized activity in the orbital cortex. In 1949, MacLean and Pribram stimulated the vagus nerve and recorded electroencephalograms from the cortical surface of anesthetized monkeys and found inconsistent slow waves generated from the lateral frontal cortex (Maclean 1990, p. 468). Moreover, Dell and Olson (1951) found that VNS evoked a slow-wave response in the anterior rhinal sulcus, *as well as in the amygdala,* in awake cats with high cervical spinal section.

Reasoning from this body of literature, Zabara demonstrated the anticonvulsant action of VNS on experimental seizures in dogs (Zabara 1985a, 1985b). Although the vagus is an autonomic nerve, Zabara, basing his conclusions on known anatomy, hypothesized that VNS could prevent or control the motor, autonomic, and conscious components of epilepsy. Interestingly, he also observed that the inhibitory effect on seizures outlasted the VNS period by approximately a factor of four in the acute model, and probably would be much longer in a chronic model. Zabara (1992) initially hypothesized that VNS had two distinct antiepileptic mechanisms of action: 1) a direct inhibition terminating the beginning or ongoing seizure and 2) a long-lasting inhibition that increased with continued periods of stimulation to prevent seizures. Dr. Kiffin Penry (Penry and Dean 1990) and others (Rutecki 1990) ushered in the modern use of VNS with the first human implant for the treatment of epilepsy in 1988.

Vagus Nerve Anatomy

Traditionally the vagus nerve has been considered a parasympathetic efferent nerve (controlling and regulating autonomic functions such as heart rate and gastric tone); however, the vagus (cranial nerve X) is actually a mixed nerve composed of about 80% afferent sensory fibers carrying information to the brain from the head, neck, thorax, and abdomen (Foley and DuBois 1937). The sensory afferent cell bodies of the vagus reside in the nodose ganglion and relay information to the NTS. These fibers are different from those that go to the other motor nuclei of the vagus (Figure 1).

The NTS relays this incoming sensory information to the rest of the brain through three main pathways: 1) an autonomic feedback loop, 2) direct projections to the

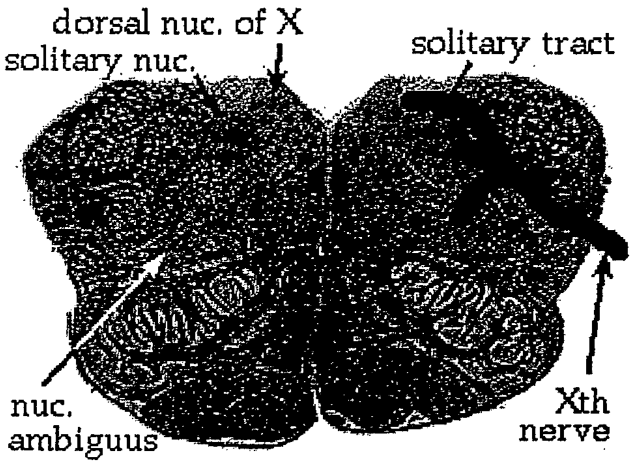

Figure 1. This cross-sectional view of the brainstem illustrates the origins of several components of the vagus nerve, a mixed sensory and motor nerve. Efferent motor fibers originate in the dorsal nucleus of the vagus, whereas afferent motor fibers go to the nucleus ambiguous. Afferent sensory fibers, which make up 80% of the left vagus, terminate in the nucleus of the solitary tract, which then projects to the midline raphe and locus and likely is the path by which vagus nerve stimulation has antiseizure and other neuropsychiatric effects.

reticular formation in the medulla, and 3) ascending projections to the forebrain largely through the parabrachial nucleus (PB) and the locus ceruleus (LC). The PB sits adjacent to the LC (one of the primary norepinephrine-containing areas of the brain; Figure 2). In fact, lesioning

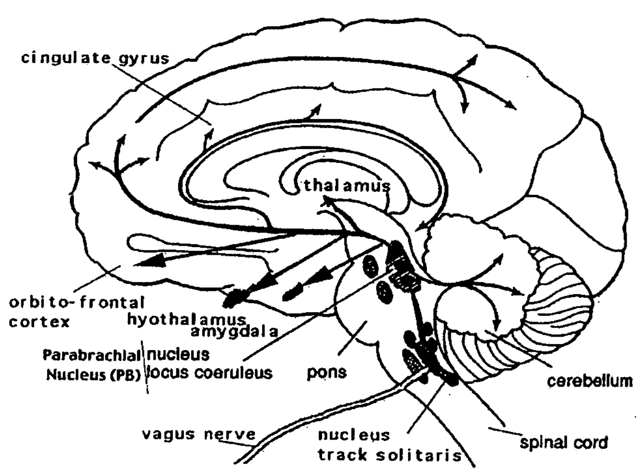

Figure 2. This diagram shows the known connections of the nucleus tractus solitarius to the parabrachial nucleus and the locus ceruleus (LC). Lesioning the LC in rats eliminates the antiepileptic properties of vagus nerve stimulation. The LC is the site of many norepinephrine-containing neurons that have important connections to the amygdala, hypothalamus, insula, thalamus, orbitofrontal cortex, and other limbic regions linked to mood and anxiety regulation.

the LC in rats eliminates the ability of VNS to suppress seizures (Krahl et al 1998), demonstrating how important this connection is for the antiepileptic action of VNS (Figure 2).

The PB/LC sends direct connections to every level of the forebrain, including the hypothalamus, and several thalamic regions that control the insula and orbitofrontal and prefrontal cortices. Perhaps important for mood regulation, the PB/LC has direct connections to the amygdala and the bed nucleus of the stria terminalis—structures that are implicated in emotion recognition and mood regulation (Van Bockstaele et al 1999; for review of the functional neuroanatomy of depression, see George et al 1997; Ketter et al 1997).

These brainstem and limbic anatomic connections have functional consequences. The oncogen C-fos is a general marker for cellular activity. C-fos studies in rats during VNS reveal increased activity in the amygdala, cingulate, LC, and hypothalamus (Naritoku et al 1995). Recently, Walker and colleagues (1999) outlined a possible role of the NTS in how VNS reduces seizures. By microinjecting the NTS with either γ-aminobutyric acid (GABA) agonists or glutamate antagonists, they found that increased GABA or decreased glutamate in the NTS blocked seizures. These findings suggest that VNS may change NTS GABA and glutamate concentrations, with secondary changes in the function of specific limbic structures noted above.

Some have suggested that because of the rotation of the body during embryonic development the left and right vagus nerves carry different information. This theory implies that the right vagus is closely associated with the cardiac atria and the left vagus with cardiac ventricular function, perhaps explaining the lack of cardiac effects of left VNS. Additionally, the NeuroCybernetic Prosthesis (NCP) System stimulating electrode is intended to be positioned below the cardiac branch of the vagus nerve. However, this line of thinking is not totally supported by early animal VNS research. There is even one patient who has been treated on the right side without complication (G.L. Morris, personal communication, October 1999). An alternative theory holds that the cardiac functional response is more a function of stimulation parameters than whether the right or left nerve is stimulated.

In sum, incoming sensory (afferent) connections of the vagus nerve provide direct projections to many of the brain regions implicated in neuropsychiatric disorders. These connections reveal how vagus nerve stimulation might be a portal to the brainstem and connected regions. These circuits likely account for the neuropsychiatric effects of VNS, and they invite additional theoretical considerations for potential research and clinical applications.

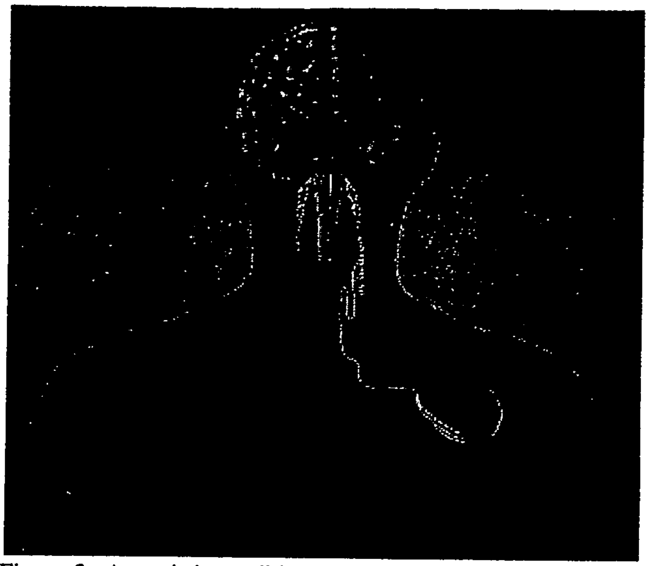

Figure 3. An artist's rendition of how the vagus is stimulated using the NeuroCybernetic Prosthesis System. A generator about the size of a pocket watch is implanted into the left chest wall. Bipolar electrodes are wrapped around the left vagus higher in the neck through a separate incision and tunneled under the skin to the generator. A physician can control the intensity and rate of generator firing by holding over the chest wall (and generator) a telemetric wand connected to a portable computer (not shown).

What Is Vagus Nerve Stimulation?

The term *vagus nerve stimulation* generally refers to several different techniques used to stimulate the vagus nerve, including those in studies in animals where the vagus was accessed through the abdomen and diaphragm. For practically all studies in humans, *Vagus Nerve Stimulation* refers to stimulation of the left cervical vagus nerve using a commercial device, the NCP System (Cyberonics, Houston; Schachter and Saper 1998; Figure 3).

Vagus Nerve Stimulation has been commercially available for the treatment of resistant partial-onset seizures in epilepsy in Europe (since 1994) and in the United States (since 1997). About 6000 people worldwide with over 7000 patient years of experience have had these generators implanted (W. Duffell, Cyberonics, personal communication). Typically, epilepsy patients considering VNS have had unsatisfactory seizure control, commonly with several medications, and for some VNS is an option before brain surgery.

In many ways, VNS delivered through the NCP System is much like the very common practice of implanting cardiac pacemakers. In both cases, a subcutaneous generator sends an electrical signal to an organ through an implanted electrode. In fact, the surgery for implanting the NCP generator in the chest is much like inserting a cardiac pacemaker (Amar et al 1998). The two techniques differ, of course, in the site of stimulation. Vagus Nerve Stimulation with the NCP System is delivered through an implantable, multiprogrammable, bipolar pulse generator (the size of a pocket watch) that is implanted in the left chest wall to deliver electrical signals to the left vagus nerve through a bipolar lead. With VNS, the electrode is wrapped around the vagus nerve in the neck, near the carotid artery using a separate incision, and connected to the generator subcutaneously. Although VNS implantation surgery was initially done almost exclusively by neurosurgeons in patients admitted overnight to a hospital and given general anesthesia, more recently some epilepsy patients have had the device implanted by vascular surgeons or ear, nose, and throat specialists via outpatient surgery with local anesthesia.

The NCP programming wand and software, along with a personal computer, provide telemetric communication with the pulse generator, which enables noninvasive programming, functional assessments (device diagnostics and interrogation), and data retrieval. The NCP System includes mechanical and electrical safety features that minimize the possibility of high-frequency stimulation that could lead to tissue damage. In addition, each patient is given a magnet that, when held over the pulse generator, turns off stimulation. When the magnet is removed, normal programmed stimulation resumes.

How Effective and Safe Is VNS in Patients with Epilepsy?

Two double-blind studies (labeled E03 [Ben-Menachem et al 1994] and E05 [Handforth et al 1998]) were conducted in patients with epilepsy, with a total of 313 treatment-resistant completers. In this difficult-to-treat group, the mean decline of overall seizure frequency was about 25–30% compared with baseline. Data from uncontrolled observations suggest that, contrary to a tolerance effect, improvement in seizure control is maintained or may improve over time (Morris et al 1999; Salinsky et al 1996). In the second controlled study (E05) of VNS in patients with epilepsy, no serious adverse events (AEs) that were judged by investigators to be probably or definitely related to VNS occurred during treatment (Handforth et al 1998; Schachter and Saper 1998). In three out of 199 patients (1.5%), infection following surgery led to device removal. Other surgery-related AEs, all of which dissipated over time, included left vocal cord paralysis (2/199 [1%]), lower facial muscle paresis (2/199 [1%]), and pain and accumulation of fluid over the pulse generator requiring aspiration (1/199 [0.5%]). The perioperative AEs reported by at least 10% of patients were pain (29%), coughing (14%), voice alteration (13%), chest pain (12%), and nausea (10%).

The AEs reported in patients in the treatment group at some time during treatment that were significantly increased from baseline were voice alteration/hoarseness, cough, throat pain, nonspecific pain, dyspnea, paresthesia,

dyspepsia, vomiting, and infection. The only AEs that occurred significantly more often in the treatment group than in the control group were dyspnea and voice alteration. Adverse events were judged to be mild or moderate 99% of the time. No cognitive, sedative, visual, affective, or coordination side effects were reported. No significant changes occurred in Holter monitoring, in the results of pulmonary function tests, or in subjects' hematology values or common chemistry values (Schachter and Saper 1998). No subjects died during the E03 or E05 controlled studies ($N = 313$). In sum, short-term AEs that are surgery related are rare and usually resolve. Stimulation-related AEs (i.e., those that occur only when the vagus nerve is stimulated) can be reduced by lowering the current level. Stimulation-related AEs can also be aborted by the patient placing a handheld magnet over the generator that turns the device off until a physician decreases the stimulation intensity. These AEs rarely lead to VNS therapy discontinuation (Morris et al 1999; Schachter and Saper 1998). Although the neurology community was initially skeptical about VNS, a recent reassessment by the American Academy of Neurology concluded that VNS for epilepsy is both "effective and safe" (Fisher and Handforth 1999).

Does VNS Affect Cardiac Function?

It is logical to carefully evaluate potential cardiac and gastrointestinal effects of vagus nerve stimulation. Cardiac evaluations have been performed on more than 250 epilepsy patients in clinical trials while receiving VNS. Holter monitoring results from clinical studies in epilepsy indicated no significant changes from baseline in cardiac function during stimulation (Handforth et al 1998).

Only during the implantation procedure itself, six cases of 10–20-sec asystole have been reported in epilepsy patients. No cases were reported in either the epilepsy or the depression clinical trials (Rush et al 2000). All six asystoles were encountered during the diagnostics test (Lead Test) stimulation—the first stimulation that a patient receives after implantation while in the operating room. The Lead Test entails approximately 15 sec of stimulation at 1.0 mA, 500 μsec, and 20 Hz of VNS. Of these six patients, three went on to have the implant (in three others the generator and leads were removed). No long-term sequelae have been reported from any asystolic events in these patients. Most importantly, no cardiac events when the device is turned on for the first time outside the operating theater have been reported in the clinic (Asconape et al 1999; Tatum et al 1999).

What about Longer Term Efficacy and Tolerability?

In patients with epilepsy, the long-term efficacy of VNS is either maintained or improved (Morris et al 1999), and the frequency of AEs generally decreases as patients accommodate to the stimulation (Salinsky et al 1996). The patient with the longest exposure to VNS has had the system operating for 10 years (W. Duffell, Cyberonics, personal communication, October 1999).

Extensive experience in epilepsy patients provides important safety data on VNS used continuously for 1 year or longer. Side effects tend to decrease over time as patients accommodate to the effects of stimulation. Two years after initial implantation over 80% of epilepsy study patients (142/172) continued with VNS, suggesting that it is well tolerated over the long term (Cyberonics 1998).

How Much Does VNS Cost, Relative to Other Treatment Modalities?

In the United States, VNS delivered with the NCP System costs roughly $9200 for the generator and electrode. The surgical and hospital costs for the implantation surgery vary widely and are more difficult to quantify but are less expensive now with the recent trend toward outpatient surgery and local anesthesia. Typically the total charge for the NCP System plus implantation varies from $12,000 to $25,000 (B. Barrett, Cyberonics, personal communication, October 1999). Most federal and private insurance companies reimburse this procedure for treatment of refractory epilepsy. After implantation the cost of the device is minimal, as the battery lasts many years and there is no required maintenance. Adjustments of the VNS settings are done by treating neurologists in their office using the personal computer and attached programming wand.

If the initial open results in depression were confirmed in a double-blind study and FDA approval granted for VNS treatment of depression, the cost of VNS would compare to about $1000 for a year of a single antidepressant medication or $10,000 to $30,000 for an acute course of ECT followed by a year of maintenance ECT (Hu and Rush 1995; Olfson et al 1998); however, since VNS is continuous and a maintenance treatment modality, true cost comparisons should be made against maintenance therapies, and the relative cost of VNS improves with each year of continued use and compares favorably to maintenance ECT, as most of the costs are associated with the initial device purchase and implantation.

Unfortunately, only a few epilepsy patients achieve full seizure remission and are able to reduce other antiepileptic medications. Most combine VNS with medications. Thus VNS, as now delivered, has not been shown to be a substitute for anticonvulsant medications. As the neuroscientific basis of VNS is better understood, there is hope that refinements of VNS settings might improve the clinical effects, with better cost savings on reductions of concomitant medications.

Rationale for Studying VNS in Mood Disorders

In addition to the neuroanatomic considerations, several additional lines of evidence provided the background for studying whether VNS might have antidepressant effects in treatment-resistant depression, culminating in the first implant for this indication in July 1998 at the Medical University of South Carolina in Charleston (Rush et al 2000), a decade after the first human epilepsy implant (Penry and Dean 1990). These hints were 1) mood effects of VNS observed in patients with epilepsy, 2) evidence by positron emission tomography (PET) scans that VNS affects the metabolism (and therefore the function) of important limbic structures, 3) the role of anticonvulsant medications in mood disorders, and 4) neurochemical studies in both animals and humans revealing that VNS alters concentrations of monoamines within the central nervous system (CNS).

Mood Effects in Epilepsy Patients

Initial uncontrolled clinical observations and, more recently, a prospective study (Harden et al 1999) and a retrospective data analysis (Elger et al, unpublished data, 1998) suggest that VNS reduces depressive symptoms in patients with epilepsy—reductions that are not entirely accounted for by reduced seizure activity. During the clinical trials of VNS for epilepsy (Ben-Menachem et al 1994; Handforth et al 1998) several investigators noted mood improvements in their patients. Although decreased seizure frequency likely accounted for some of these improvements, the clinical impression was that they went beyond those attributable to improved seizure control alone. For example, some patients with minimal or no improvement in seizure frequency also reported substantial improvements in mood. Improved quality of life was also seen, and without seizure frequency changes in some patients. Thus, while no specific measures of depressive symptoms were obtained during the epilepsy trials, these repeated reports from independent investigators suggested that VNS might be associated with significant mood improvement. This is reminiscent of the "psychotropic" effects reported in epilepsy patients treated with carbamazepine, which led to the clinical trials in mood-disordered patients (Ballenger and Post 1980). In a recent prospective study of patients with epilepsy ($N = 34$), a trend toward mood improvements was seen in the 14 who received VNS, based on the Cornell Dysthymia Rating Scale ($p < .1$; Harden et al 1999). The significant improvement in seizure frequency found in the VNS group was not related to mood changes on an individual basis. The authors suggested that VNS might improve mood independent of seizure frequency reduction.

PET Studies of Limbic Activation

In 10 patients with epilepsy who received VNS, PET measurements were taken three times before and then during VNS (Henry et al 1998). The results demonstrated increased brain blood flow from rest to during VNS in the rostral medulla, thalamus, hypothalamus, insula, and postcentral gyrus, with greater activation on the right side (contralateral to the device). In contrast, blood flow was significantly decreased during stimulation bilaterally in the hippocampus, amygdala, and cingulate gyrus. The cingulate gyrus has been repeatedly implicated in imaging studies of depression pathogenesis, and a decline in cingulate activity with antidepressant response has been seen in numerous studies (sleep deprivation [Ebert et al 1994; Wu et al 1992], selective serotonin reuptake inhibitor treatment [Mayberg et al 1997], symptom provocation with drugs [Bremner et al 1997]). Thus, VNS changes in activity of the brainstem, limbic system, and other CNS areas are compatible with antidepressant activity.

Anticonvulsants as Mood Stabilizers

A third reason for considering the role of VNS in the treatment of mood disorders is the substantial evidence that anticonvulsant medications have mood-stabilizing effects (Goodwin and Jamison 1990; Post et al 1992). Within the last 20 years, several anticonvulsants have found a role in mood stabilization (carbamazepine [Ballenger and Post 1980; Okuma et al 1973], valproic acid [Calabrese and Delucchi 1989; Swann et al 1997]) or as antidepressants in (depressed phase) bipolar disorder (lamotrogine; Fatemi et al 1997). Further, it is well established that our most effective antidepressant treatment, ECT, has powerful anticonvulsant effects (Sackeim 1999; Sackeim et al 1983). Thus, it is reasonable to hypothesize that an effective antiepileptic device might also have antidepressant or mood-stabilizing effects.

Neurochemical Changes

The basic mechanisms of action of VNS are unknown. However, both clinical and animal studies indicate that VNS likely results in changes in serotonin (Ben-Menachem et al 1995), norepinephrine (Krahl et al 1998), GABA, and glutamate (Walker et al 1999)—neurotransmitters implicated in the pathogenesis of major depression. Vagus nerve stimulation in animals activates the LC, the main source of CNS norepinephrine-containing neuronal cell bodies (Naritoku et al 1995). In patients with epilepsy, VNS appears to increase cerebrospinal fluid 5-hydroxyindoleacetic acid—a metabolite of serotonin (Ben-Menachem et al 1995). Since many of the currently available therapies are believed to work using the same neurotrans-

mitters (serotonin or norepineprine), it was hypothesized that VNS might also have antidepressant activity.

Further, there is a long history of autonomic nervous system dysfunction in depressed patients, which is mediated by the vagus nerve. These abnormalities include differences in heart rate variability (for review, see Glassman 1998). Thus, if depressed patients have abnormalities in brain regions that control the vagus nerve (top-down regulation), then stimulating the vagus nerve might theoretically engage this dysfunctional circuit (a bottom-up approach).

Summary

Several lines of evidence pointed toward the possible benefit of VNS as an antidepressant or mood-stabilizing treatment. These included clinical observations in epilepsy patients, anatomic afferent connections of the left vagus nerve to the CNS and to structures relevant to mood regulation, the anticonvulsant activity of VNS taken in the context of the role of anticonvulsant medications or ECT in treating mood disorders, neurochemical studies indicating VNS effects on key neurotransmitters involved in mood regulation, and evidence that VNS changes the metabolic activity of key limbic system structures. This evidence led to the initial open trial described in the companion article in this journal (Rush et al 2000).

Other Areas of Potential Research or Clinical Promise with VNS

Work to date has established that VNS is an effective anticonvulsant. Recent work suggests that VNS may have antidepressant properties. The vagus nerve is an important route of information into the CNS. Several theories of the anxiety disorders posit either a faulty interpretation of peripheral information into the CNS or erratic availability of same (Gray 1982; James 1884; Watkins et al 1998). It is conceivable that altering the flow of this information with VNS could have therapeutic potential in anxiety disorders (e.g., generalized anxiety disorder, panic disorder) or irritable bowel syndrome.

Similarly, the vagus contains information about hunger, satiety, and pain. Potential studies in the areas of treatment-resistant obesity, addictions, and pain syndromes are also theoretically justified. Moreover, the NTS sends fibers into the dorsal raphe and areas that are known to control levels of alertness. Thus, VNS might be considered as a potential treatment for some disorders of sleep or alertness like coma or narcolepsy. For example, a recent study in 10 epilepsy patients found that high-intensity, high-frequency VNS reduced total time in rapid eye movement sleep, and such sleep was less fragmented (Vaugh and D'Cruz 1999). Therefore, in addition to advancing our understanding of the pathophysiology of various neuropsychiatric disorders, VNS may have other therapeutic applications, which are guided by the known anatomy of vagus connections.

A recent study by Clark and colleagues hints at the potential for VNS to be used to investigate brain circuits involved in memory and learning (Clark et al 1999). These researchers examined word-recognition memory in 10 patients enrolled in a clinical study of VNS for epilepsy. Vagus stimulation administered after learning and during memory consolidation caused intensity-dependent enhancement of word recognition relative to sham stimulation. Other work has shown that vagotomy attenuates the memory-enhancing properties of amphetamine.

Further Refinements in the Use of VNS

At present, the delivery of VNS involves a surgical procedure that includes exposure and manipulation of the carotid artery, as well as the cosmetic and other inconveniences of having a generator in the chest wall. As a consequence, the NCP System is typically used in those patients who have not responded to other therapies. In both epilepsy and depression, some patients will receive little to no benefit, despite having had surgery. The development of less invasive ways of delivering VNS or predicting which patients will benefit would likely expand the clinical potential of VNS. Preliminary attempts at externally stimulating the vagus nerve via a transcranial magnetic stimulator have not been successful, in part due to the difficulty of finding a reliable indication of whether TMS has activated the vagus (H. Sackeim et al, unpublished data, April 1998). Another possibility might be to develop a temporary percutaneous method of stimulation.

Yet a different approach would be to identify the subset of patients who are most likely to benefit from VNS, by using functional neuroimaging or other measures. In this context, a recent PET study in adults with epilepsy found that increased blood flow in the right and left thalamus during the initial VNS stimulation correlated with decreased seizures over the next few weeks (Henry et al 1999). This finding suggests that one could use functional imaging, combined with VNS, to select patients most likely to benefit from this therapy.

Finally, VNS can be delivered at different amplitudes and frequencies and with different pulse widths, all at various duty cycles (ratio of "on" time to "off" time). More basic work would advance this area through an understanding of how varying combinations of these parameters affect different brain regions or influence different neuropsychiatric conditions. It seems logical to suggest that VNS delivered with parameters different from

those commonly used for epilepsy might produce different CNS effects that would in turn broaden the clinical indications.

Conclusion

Vagus nerve stimulation, one of the newest methods to physically alter brain function, builds on a long history of investigation of the relationship of autonomic signals with limbic and cortical function. Vagus nerve stimulation is already established as a clinically useful anticonvulsant in patients with resistant epilepsy and may have promise as an antidepressant treatment. The known anatomic projections of the vagus nerve suggest that VNS might also have other neuropsychiatric applications. Further research is needed to clarify the mechanisms of action of VNS and the potential clinical utility of this intriguing new somatic portal into the CNS.

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